# Prognostic value of estimated plasma volume in heart failure

Kévin Duarte, Jean-Marie Monnez, Eliane Albuisson, Bertram Pitt, Faiez Zannad, Patrick Rossignol

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Duarte K (MSc)[1, 2, 3], Monnez JM (PhD)[1, 2, 3], Albuisson E (MD, PhD)[1, 2, 4, 5, 6], Pitt B (MD)[7], Zannad F (MD, PhD)[5, 8, 9, 10, 11], Rossignol P (MD, PhD)[5, 8, 9, 11]

1. Université de Lorraine, Institut Elie Cartan de Lorraine, UMR 7502, Vandoeuvre-lès-Nancy, F-54506, France
2. CNRS, Institut Elie Cartan de Lorraine, UMR 7502, Vandoeuvre-lès-Nancy, F-54506, France
3. Team BIGS, INRIA, Villers-lès-Nancy, F-54600, France.
4. CHU Nancy, Pôle S²R, PARC, ESPRI-BIOBASE, Vandoeuvre-lès-Nancy, France
5. Inserm, Centre d'Investigations Cliniques-Plurithématique 1433
6. Université de Lorraine, Faculté de Médecine, SPI-EAO, Vandoeuvre-lès-Nancy, France
7. University of Michigan School of Medicine, Ann Arbor, Michigan, USA.
8. Inserm U1116, Nancy, France
9. Université de Lorraine, France
10. CHU Nancy, Pôle de Cardiologie, Institut Lorrain du Cœur et des Vaisseaux, Vandoeuvre-lès-Nancy, France
11. F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France

**Brief title**: prognostic value of estimated plasma volume in HF

**Conflict of interest**

Patrick Rossignol received travel grants from Pfizer Inc; Bertram Pitt and Faiez Zannad received remuneration from Pfizer as members of the EPHESUS Executive Steering Committee. Faiez Zannad and Patrick Rossignol are CardioRenal diagnosticS co-founders. The remaining authors report no conflicts.

**Corresponding author**: P. Rossignol
Centre d'Investigations Cliniques-INSERM CHU de Nancy
Institut lorrain du Cœur et des Vaisseaux Louis Mathieu
4 rue du Morvan
54500 Vandoeuvre Lès Nancy
France
Tel : +33 3 83 15 73 20
Fax : +33 3 83 15 73 24
p.rossignol@chu-nancy.fr

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**Abstract**

**Objectives:** To assess the prognostic value of the estimation of plasma volume, or of their variation beyond clinical examination in a *post-hoc* analysis of the Eplerenone Post-Acute Myocardial Infarction (AMI) Heart Failure (HF) Efficacy and Survival Study (EPHESUS).

**Background**: Assessing congestion post-discharge is challenging but of paramount importance to optimize patient management and to prevent hospital readmissions.

**Methods:** The present analysis was performed in a subset of 4957 patients with available data (within a full dataset of 6632 patients). Study endpoint was cardiovascular death and/or hospitalization for HF between month 1 and month 3 after post-AMI HF. Estimated plasma volume variation (ΔePVS) between baseline and month 1 was estimated by the Strauss formula, which includes hemoglobin and hematocrit ratios. Other potential predictors including congestion surrogates, hemodynamic and renal variables, and medical history variables were tested. An instantaneous estimation of plasma volume at month 1, ePVS M1, was defined and also tested.

**Results:** Multivariate analysis was performed using stepwise logistic regression. ΔePVS was selected in the model (OR=1.01, p=0.004). The corresponding prognostic gain measured by integrated discrimination improvement (IDI) was significant (7.57 %, p=0.01). Nevertheless, ePVS M1 was found to be a better predictor than ΔePVS.

**Conclusion**: In HF complicating MI, congestion as assessed by the Strauss formula and an instantaneous derived measurement of plasma volume provided a predictive value of early cardiovascular events, beyond routine clinical assessment. Prospective trials assessing congestion management guided by this simple tool to monitor plasma volume are warranted.

**Key words**: plasma volume, heart failure, congestion

**Condensed abstract:** In heart failure complicating myocardial infarction, congestion assessed by the Strauss formula and an instantaneous derived measurement of plasma volume provided a prediction of early cardiovascular events beyond routine clinical assessment. Trials assessing congestion management guided by this simple tool to monitor plasma volume are warranted.

**Abbreviations**

HF: heart failure

PV: plasma volume

BP: blood pressure

LVEF: left ventricular ejection fraction

AMI: acute myocardial infarction

eGFR: estimated glomerular filtration rate

LR: logistic regression

LDA: linear discriminant analysis

## Introduction

Congestion is the major cause for heart failure (HF) hospitalization. However, many HF patients are discharged with persistent signs and symptoms of congestion, high left ventricular filling pressures[1] and evidence of hypervolemia[2]. Available data suggest that a pre-discharge clinical assessment of congestion is often not performed, and even if performed is not done systematically[1]. The same issue arises after discharge and may contribute to the burden of rehospitalizations. Careful evaluation of all physical findings, laboratory variables, weight change and net fluid change is warranted before discharge, as suggested by guidelines[3]. Among readily available data at discharge biological surrogates of plasma volume and therefore of congestion have been shown to be associated with post-discharge outcomes[4-8]. Plasma volume may be assessed indirectly using several published methods. Whether these various methods of plasma volume measurement beyond clinical examination have different prognostic value is unknown and was therefore investigated in this study using data from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).

## Methods

### Population

The design and results of the trial have been reported previously[9]. The EPHESUS study enrolled 6632 patients with HF following acute myocardial infarction (AMI) complicated by left ventricular systolic dysfunction (ejection fraction $\leq 40\%$). HF had to be documented by at least one of the following: presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound. Clinical signs of pulmonary congestion were not required at inclusion in patients with diabetes mellitus. Patients were entered into the study from 3 to 14 days post infarction (with inclusion (M0) performed pre-discharge in 80% of patients). All patients were randomly assigned to

treatment with eplerenone 25 mg/day or placebo. EPHESUS was an event-driven study with a mean duration of follow-up of 16 months. Clinical assessments were made at inclusion (M0), at month 1 (M1), at month 3 (M3), and every three months thereafter. Among the 6632 patients included in the EPHESUS study, 1675 were excluded from the analysis because of unavailable data at baseline and/or at month 1 (259 died before 5 weeks and 1416 did not have the clinical and/or biological data required for all the analyses conducted in the present study). The present analysis was therefore performed on the 4957 remaining patients.

**Study end points**

The aim of the present study was to predict early cardiovascular events i.e. cardiovascular death and/or hospitalization for HF (the primary endpoint of the study, adjudicated by a blinded critical event committee, as per trial protocol[9]) between 1 month and 3 months after AMI with HF (including a sensitivity analysis performed at 6 months in the study population with available hemoglobin and hematocrit data at M0).

**Estimation of change in plasma volume**

To estimate relative changes in plasma volume (PV) between M0 and M1 three different formulas were tested. The Strauss formula (ΔePVS) uses changes in hemoglobin and hematocrit concentrations and does not provide an instantaneous measure of PV but estimates its change between two time points[10-12], while the Kaplan and Hakim formulas respectively estimate instantaneous PV taking into account weight and hematocrit concentration at a given time point [11, 13, 14] . The only formula associated with cardiovascular events in this analysis (*see online data supplements: complete statistical section and Table 1*) was the Strauss formula, defined by: $\Delta ePVS = 100 \times \frac{\text{hemoglobin(M0)}}{\text{hemoglobin(M1)}} \times \frac{1 - \text{hematocrit(M1)}}{1 - \text{hematocrit(M0)}} - 100$

This formula can be interpreted as the relative change in estimated plasma volume between M0 and M1. For this reason, ePVS was defined as being proportional to this value.

The instantaneous formula for estimating PV, derived from ΔePVS is:

$$\text{ePVS} = \frac{1 - \text{hematocrit}}{\text{hemoglobin}(\text{g}/\text{dL})} \times 0.01$$

**Variables**

Measurements at M0 and M1 included ePVS, NYHA stage, KILLIP class (available at M0 only), weight, estimated glomerular filtration rate (eGFR) assessed by the MDRD formula[15], blood pressure (BP), hemoglobin and hematocrit concentrations, serum sodium, left ventricular ejection fraction (LVEF) (available at M0 only). ΔePVS and change in the continuous variables between M0 and M1 were also considered together with medical history (age, sex, race, previous hospitalization for HF, reperfusion therapy, previous AMI, diabetes, prior episodes of HF and hypertension). Owing to the number of missing values of albumin and serum protein at M0 and M1 (25%), these variables were not considered in the present analysis. Both were associated with outcomes as well as albumin but not the change in serum protein in univariate analysis (data not shown).

**Concise Statistical Analysis section** *(a complete description is provided as an online data supplement)*

All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina) and R software (R Development Core Team, 2005). Continuous variables are described as median and interquartile range, and categorical data as proportions. The Chi-square test or Fisher's exact test was used for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. Correlations were obtained with Spearman's rho. The 2-tailed significance level was set to $p \leq 0.05$.

In order to select a set of predictors for multivariate analysis, a univariate analysis was performed to test the existence of a significant dependence between each of the initial variables and the two-class variable "event / non-event". A variable was retained if the corresponding p-value was smaller than 0.15 which is commonly used in such approaches. Moreover, any variable highly correlated with another variable and with a less significant p-value was not retained.

To examine association with event, a stepwise logistic regression based on the remaining variables was performed by using the likelihood ratio test at a threshold of 0.05. This analysis automatically excluded insufficiently predictive variables. Prognostic gain of ΔePVS or ePVS was assessed by the integrated discrimination improvement (IDI), the continuous net reclassification improvement (NRI) and the increased area under ROC curve (IAUC). Stepwise discriminant analysis and linear discriminant analysis (LDA) were also performed to verify the stability of the set of retained variables (*online data supplements, Table 2*). Furthermore, the quality and stability of all models were tested by cross-validation (*online data supplements, Table 3*). Finally, subgroup analyses were performed using a stepwise logistic regression: with and without anemia, anticoagulants, antithrombotic and reperfusion therapy at baseline. Anemia was defined according to the World Health Organization (WHO) criteria as a baseline hemoglobin < 13g/dL for men and < 12 g/dL for women.

**Results**

Comparison of the characteristics at baseline between included and non-included patients shows that the 1675 non-included patients generally had more severe HF (*Table 1*).

**Baseline, 1-month, and in-between features associated with cardiovascular events in univariate analysis**

Patients with events (*Table 2*) were older and had a lower LVEF, weight and eGFR at baseline and M1, as well as higher NYHA and KILLIP classes, lower hemoglobin and hematocrit concentrations.

ΔePVS was significantly associated with early cardiovascular (CV) events (p=0.0009). Of note, ePVS at baseline and M1 were also significantly associated with CV events (p<0.0001). Patients losing weight experienced more frequent events. Of note, ΔePVS and changes in body weight were not significantly correlated (rho=0.02; p=0.093).

**Multivariate analysis including ΔePVS**

ΔePVS was retained in the logistic regression model (OR=1.01, p=0.004) (Table 3): if plasma volume increased, the probability of CV event also increased.

With regard to the added predictive ability of ΔePVS in the model beyond clinical variables, both NRI and IAUC measures were positive but not significant: NRI=0.09 (p=0.18), IAUC=0.0012 (p=0.39). ΔePVS significantly improved the IDI by 7.57 % (p=0.01).

Of note, in a sensitivity analysis in the subgroups with and without anemia, ΔePVS was also retained in the models (*online data supplements, Table 4*).

**Multivariate analysis including the instantaneous ePVS**

ePVS at M1 was retained in the logistic regression model (OR=1.38, p<0.0001) (*Table 4*). The three measures of added predictive ability of ePVS at M1 were positive and significant: relative IDI = 15.06 % (p=0.004), NRI=0.18 (p=0.004), IAUC=0.01 (p=0.035).

With regard to sensitivity analyses: i) ePVS M1 was a better predictor of early cardiovascular events than ΔePVS (online data supplements). ii) In the subgroups with and without anemia at baseline, ePVS M1 was retained in the models as was the case in the subgroups with and without anticoagulants, antithrombotics and reperfusion therapy at baseline (*online data*

*supplements, Table 4*). iii) In a larger EPHESUS dataset (i.e. which included 5845 or 5880 patients with available hemoglobin or hematocrit measurements at M0), ePVS M0 was only marginally associated with event occurrence at M1 (p=0.051), whereas it was significantly associated with 90-day events (OR=1.12, p=0.007; NRI: p=0.027; IDI: p=0.075) and 180-day events (OR=1.14, p=0.0006; NRI: p=0.0003; IDI: p=0.002). Of note, when ePVS M1 was considered in lieu of ePVS M0, it was retained in the model (p<0.0001) and significantly increased the predictive capacity of the model (data not shown). iv) In a subset of the EPHESUS population with available Brain Natriuretic Peptide (BNP) measurements, we previously reported significant positive correlations between changes in BNP and plasma volume, as assessed by the Strauss Formula between baseline and month 1[5]. Present analysis of this subset of 346 patients showed that BNP and instantaneous ePVS at M0 and M1 were significantly but weakly correlated (rho=0.23, p<0.0001 at M0, and 0.25, p<0.0001 at M1). Among this subset, 14 patients experienced a CV event. BNP M1 (AUC=0.88) and ePVS M1 (AUC=0.78) were good predictors of CV events in univariate analysis although the model had an even greater discriminative ability when both variables were combined (AUC=0.90) (*Figure 1*). With regard to the added predictive ability of ePVS M1 in the model including both variables, the three measures were positive and only IAUC was not significant: relative IDI=129.9% (p=0.029), NRI=0.89 (p=0.0006), IAUC=0.02 (p=0.36). However, owing to the small number of CV events, these last results should be interpreted with caution,

**Discussion**

To our knowledge, the results of this analysis show for the first time that in patients with HF and left ventricular systolic dysfunction complicating AMI a short-term (one month) decrease in estimated plasma volume using the Strauss formula (i.e. decongestion) was associated with better cardiovascular outcomes independent from the clinical variables used in routine practice (e.g. NYHA, KILLIP class, body weight, BP, LVEF, eGFR). Moreover, we found

that an instantaneous estimation of plasma volume directly derived from the Strauss formula displayed greater prognostic value. An instantaneous plasma volume estimation should enable physicians to immediately and reliably assess the patient's congestive status beyond usual routine clinical assessment and natriuretic peptide measurement.

The non-invasive assessment of plasma volume is important in the management of HF patients to tailor diuretic doses to the needs of the individual patient, as recommended by all current guidelines[3, 16] but often not achieved due to the unreliability of clinical signs and symptoms. In the present study a majority of patients received loop diuretics at baseline, with these patients experiencing more events. Of note, observational studies have shown an association between high-dose loop diuretics and adverse outcomes. However, these studies are confounded by the fact that patients receiving higher doses of diuretics tend to have greater disease severity and/or comorbidity[17]. In the present series decongestion between baseline and at one-month, as assessed by a decrease in estimated plasma volume, was found to be associated with better clinical outcomes. This finding corroborates and extends data derived from 3 randomized trials in acute decompensated HF reporting an association between decongestion (as assessed by biological surrogates of plasma volume) during index hospitalization and better outcomes. An analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial investigated baseline-to-discharge increases in hematocrit, albumin and total protein values. Patients with values $\geq 2$ among the three aforementioned variables in the top tertile were considered to have evidence of hemoconcentration, which was associated with greater net weight/fluid loss and greater reductions in right atrial pressure and pulmonary capillary wedge pressure, along with a substantially lower risk of mortality[4]. In an analysis of the PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure

and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study, hemoconcentration was defined as an increase in hemoglobin levels between baseline and day 7 in patients presenting with acute decompensated HF. A rapid increase in hemoglobin during hospitalization was related to improved 180-day survival[6]. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, analysis of the absolute in-hospital hematocrit changes calculated between baseline and discharge or day 7 (whichever occurred first) showed that patients with hemoconcentration (i.e. ≥ 3% absolute increase in hematocrit) were less likely to have clinical congestion at discharge, while every 5% increase in in-hospital hematocrit change was associated with decreased cardiovascular mortality or HF hospitalization at ≤ 100 days post randomization[7].

The present study, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), provided an opportunity to monitor decongestion whilst using both clinical and biological variables after discharge, between baseline and one month, a critical time frame in terms of rehospitalization burden. Several formulas were used to estimate instantaneous plasma volume and respective changes between baseline and one-month post-myocardial infarction in patients with HF. In a head-to-head comparison during univariate analysis, only the Strauss formula (to assess variations) and its instantaneous derivation were associated with 3–month outcomes. This formula contains hemoglobin ratios and therefore includes both hemoglobin changes, which may be relevant in HF patients with the cardiorenal anemia syndrome[18], and multifactorial changes involving medications as well as bone marrow dysfunction associated with kidney dysfunction, inflammation and malnutrition. Although both hematocrit and hemoglobin and their respective changes were also associated with outcomes under univariate analysis, they were not considered in the multivariate analysis, owing to the collinearity with plasma volume estimation and to the uncertainty related to the relative contribution of congestion and anemia in these variables.

Hemoconcentration, as evidenced by a rising hematocrit, is an appropriate surrogate indicating that the plasma refill rate has been exceeded by the rate of fluid removal, which can be easily and continuously measured by using an in-line hematocrit sensor during ultrafiltration therapy[19]. Importantly, however, in the subgroups with and without anemia at baseline, ΔePVS or ePVS at M1 were always retained in the multivariate models. The fact that both the Kaplan and Hakim formulas were not associated with outcomes may arise from the integration of body weight in both formulas. Indeed, both Kaplan and Hakim ePV increase when hematocrit decreases and conversely decrease when weight decreases, while patients with events displayed lower weight and hemoglobin. Ideally, dry weights (i.e. the body weight measured in non-congested patients), not assessed in the present study and difficult to estimate in routine practice owing to frequently persisting edema in HF patients, should have been used to run these two formulas. Moreover, body weight loss, which was found to be associated with worse outcomes, may rather be associated with cachexia[20-22], as opposed to decongestion, and therefore may be misleading for monitoring congestive status.

Several limitations should be acknowledged in the present study. First, the analysis in the EPHESUS patient population was performed in myocardial infarction patients with HF and altered ejection fraction and, thus, the external validity of these results remains to be assessed in other patient populations. In any event, the present results are hypotheses-generating stemming from a *post-hoc* analysis and should be confirmed by further prospective investigations. Of importance, we believe that the statistical results are robust, considering that two different methods of discrimination (LR and LDA) were used to create an event prediction model in order to verify the consistency of the results. Finally, the stability of the models was tested by performing cross-validations with ΔePVS or ePVS being consistently selected in the models.

Secondly, changes in plasma volume, as estimated by the Strauss formula, were assessed by a proposed[10] indirect estimation of plasma volume changes. This is a validated (upon comparison with a radiolabeled gold standard) method integrating hematocrit changes which is routinely used to estimate plasma volume in patients with scheduled plasma exchanges[23, 24], or even ultrafiltration in the HF setting[25], whereas notably no specific validation has been reported to date in the HF setting. Interestingly, a sensitivity analysis showed that BNP (as a surrogate of cardiac congestion) measured in 346 patients and instantaneous ePVS were significantly but weakly correlated, and that the coexistence of both elevated BNP and elevated instantaneous ePVS at month 1 was more prone to predict worse outcomes than either alone, which further strengthens the pathophysiological relevance of plasma volume estimation beyond the usual tools.

In conclusion, in the setting of HF complicating AMI, our data provide important insights related to congestion assessment and its post discharge prognostic value, using a simple estimation of plasma volume (with the Strauss formula or its instantaneous derivate) beyond usual clinical variables which may therefore have major clinical implications for patient management. We suggest that monitoring plasma changes in volume may be useful to guide therapy optimization in patients after discharge from a HF hospitalization which remains an important unmet need. Dedicated prospective outcome studies evaluating the role of the Strauss formula to estimate changes in plasma volume are warranted.

**Clinical perspectives**

Competency in Medical Knowledge: the use of a simple tool to estimate plasma volume may enable to better detect congestion in heart failure patients

**Translational outlook** Dedicated prospective outcome studies are warranted to determine whether such estimation may be useful to guide therapy optimization

**REFERENCES**


1. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G. Assessing and grading congestion in acute heart failure: A scientific statement from the acute heart failure committee of the heart failure association of the european society of cardiology and endorsed by the european society of intensive care medicine. *Eur J Heart Fail*. 2010;12:423-433
2. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: Role for blood volume quantitation. JACC Heart Fail. 2014;2:298-305
3. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, Casey DE, Jr., McMurray JJ, Drazner MH, Mitchell JE, Fonarow GC, Peterson PN, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239
4. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265-272
5. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an ephesus (eplerenone post-acute myocardial infarction heart failure efficacy and survival study) substudy. *J Am Coll Cardiol*. 2011;58:1958-1966
6. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013; 61:1973–81
7. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, Maggioni AP, Nodari S, Konstam MA, Butler J, Filippatos G. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: Insights from the everest trial. *Eur J Heart Fail*. 2013 ; 15:1401-11
8. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: Importance of sustained decongestion. *J Am Coll Cardiol*. 2013;62:516-524
9. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-1321
10. Strauss MB, Davis RK, Rosenbaum JD, Rossmeisl EC. Water diuresis produced during recumbency by the intravenous infusion of isotonic saline solution. *J Clin Invest*. 1951;30:862-868
11. Kalra PR, Anagnostopoulos C, Bolger AP, Coats AJ, Anker SD. The regulation and measurement of plasma volume in heart failure. *J Am Coll Cardiol*. 2002;39:1901-1908

12. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol*. 1974;37:247-248
13. Kaplan AA. A simple and accurate method for prescribing plasma exchange. *ASAIO Trans*. 1990;36:M597-599
14. Hakim RM, Neyra R, Ismail N. Plasmapheresis. *Handbook of dialysis*.248:280
15. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137-147
16. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (hfa) of the esc. *Eur Heart J*. 2012;14:803-869
17. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail*. 2014;16:471-482
18. Davenport A, Anker SD, Mebazaa A, Palazzuoli A, Vescovo G, Bellomo R, Ponikowski P, Aspromonte N, Bagshaw S, Berl T, Daliento L, Haapio M, Hillege H, McCullough P, Katz N, Maisel A, Mankad S, Zanco P, Ronco F, Shaw A, Sheinfeld G, Soni S, Zamperetti N, Ronco C. Adqi 7: The clinical management of the cardio-renal syndromes: Work group statements from the 7th adqi consensus conference. *Nephrol Dial Transplant*. 2010;25:2077-2089
19. Boyle A, Sobotka PA. Redefining the therapeutic objective in decompensated heart failure: Hemoconcentration as a surrogate for plasma refill rate. *J Card Fail*. 2006;12:247-249
20. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet*. 1997;349:1050-1053
21. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: An observational study. *Lancet*. 2003;361:1077-1083
22. Pocock SJ, McMurray JJ, Dobson J, Yusuf S, Granger CB, Michelson EL, Ostergren J, Pfeffer MA, Solomon SD, Anker SD, Swedberg KB. Weight loss and mortality risk in patients with chronic heart failure in the candesartan in heart failure: Assessment of reduction in mortality and morbidity (charm) programme. *Eur Heart J*. 2008;29:2641-2650
23. Buffaloe GW, Heineken FG. Plasma volume nomograms for use in therapeutic plasma exchange. *Transfusion*. 1983;23:355-357

24. Sprenger KB, Huber K, Kratz W, Henze E. Nomograms for the prediction of patient's plasma volume in plasma exchange therapy from height, weight, and hematocrit. *J Clin Apher*. 1987;3:185-190
25. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol*. 2001;38:963-968

**Figure legends**

**Figure 1**:

**Title**: ROC curves related to BNP and ePVS measurements at Month 1.

**Caption**: ROC curves from univariate and multivariate logistic regression in the subset of the study population (n= 346, 14 with CV events) with available BNP and ePVS measurements at M1.

# Tables

**Table 1 : Baseline characteristics between included and non-included patients**

| Variables | Included n=4957 | Non-included n=1675 or less (indicated) | p |
|---|---|---|---|
| NYHA ≥ 2 | 70 | 71 (n=1326) | 0.53 |
| NYHA ≥ 3 | 17 | 22 (n=1326) | **<.0001** |
| KILLIP ≥ 2 | 85 | 83 (n=1634) | 0.067 |
| KILLIP ≥ 3 | 19 | 22 (n=1634) | **0.030** |
| Weight (kg) | 77 [19] | 76 [18] (n=1671) | 0.19 |
| eGFR (mL/min/1.73 m²) | 68 [26] | 65 [28] (n=1406) | **0.0008** |
| Systolic BP (mmHg) | 120 [20] | 115 [24] (n=1673) | **<.0001** |
| Diastolic BP (mmHg) | 70 [15] | 70 [18] (n=1673) | **0.0003** |
| Hemoglobin (g/dL) | 13.4 [2.2] | 13.2 [2.5] (n=1599) | **<.0001** |
| Hematocrit (%) | 40 [6] | 39 [7] (n=1534) | **0.0004** |
| Sodium (mmol/L) | 140 [5] | 139 [6] (n=1637) | **<.0001** |
| LVEF (%) | 35 [8] | 34 [8] (n=1660) | **<.0001** |
| **Medical history** | | | |
| Age (years) | 65 [17] | 65 [19] | 0.36 |
| Male | 71 | 72 | 0.16 |
| Caucasian | 91 | 89 | **0.016** |
| Hospitalization for HF | 7 | 9 | 0.12 |
| Reperfusion therapy | 46 | 44 | 0.19 |
| Previous AMI | 27 | 28 | 0.29 |
| Diabetes | 31 | 36 | **0.0001** |
| Prior episodes of HF | 14 | 15 | 0.35 |
| Hypertension | 61 | 58 | **0.011** |
| **Medications** | | | |
| Eplerenone | 50 | 50 | 0.90 |
| ACEI / ARB | 86 | 88 | 0.14 |
| Beta-blockers | 76 | 72 | **0.001** |
| Loop diuretics | 54 | 59 | **0.0001** |

Values are expressed as medians [inter-quartile range] or proportions (%), where appropriate. ACEI: Angiotensin-converting enzyme inhibitor**,** AMI: acute myocardial infarction, ARB: angiotensin receptor blocker, BP: blood pressure, eGFR: estimated glomerular filtration rate, ePV: estimated plasma volume, HF: heart failure, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association functional class.

**Table 2: Characteristics of patients with and without events**

| Variables | Non-event n=4697 | Event n=260 | p |
|---|---|---|---|
| NYHA M0 ≥ 2 | 70 | 77 | **0.013** |
| NYHA M0 ≥ 3 | 16 | 34 | **<.0001** |
| NYHA M1 ≥ 2 | 66 | 81 | **<.0001** |
| NYHA M1 ≥ 3 | 13 | 37 | **<.0001** |
| KILLIP M0 ≥ 2 | 85 | 91 | **0.008** |
| KILLIP M0 ≥ 3 | 18 | 34 | **<.0001** |
| Weight M0 (kg) | 78 [19] | 74[17] | **0.003** |
| Weight M1 (kg) | 77 [19] | 74 [17] | **0.0005** |
| Δ Weight (kg) * | 0 [3] | -1 [3] | **0.014** |
| Δ ePVS (%) | -2 [20] | 0 [21] | **0.0009** |
| ePVS M0 | 4.478 [1.189] | 4.701 [1.269] | **<.0001** |
| ePVS M1 | 4.348 [0.978] | 4.711 [1.321] | **<.0001** |
| eGFR M0 (mL/min/1.73 m²) | 68 [26] | 62 [26] | **<.0001** |
| eGFR M1 (mL/min/1.73 m²) | 67 [25] | 57 [27] | **<.0001** |
| Δ eGFR (mL/min/1.73 m²) * | 0 [17] | -3 [19] | **0.015** |
| Systolic BP M0 (mmHg) | 120 [20] | 118 [24] | 0.22 |
| Systolic BP M1 (mmHg) | 120 [30] | 120 [28] | **0.022** |
| Δ Systolic BP (mmHg) * | 5 [22] | 3 [20] | **0.14** |
| Diastolic BP M0 (mmHg) | 70 [15] | 70 [16] | **0.042** |
| Diastolic BP M1 (mmHg) | 76 [10] | 75 [12] | **0.061** |
| Δ Diastolic BP (mmHg) * | 0 [15] | 0 [15] | 0.75 |
| Hemoglobin M0 (g/dL) | 13.4 [2.2] | 12.9 [2.1] | **<.0001** |
| Hemoglobin M1 (g/dL) | 13.6 [1.9] | 12.9 [2.2] | **<.0001** |
| Δ Hemoglobin (g/dL) * | 0.2 [1.6] | 0 [1.9] | **0.001** |
| Hematocrit M0 (%) | 40 [6] | 39 [6] | **0.0001** |
| Hematocrit M1 (%) | 41 [5] | 39 [6] | **<.0001** |
| Δ Hematocrit (%)* | 1 [5] | 0 [5] | **0.002** |
| Sodium M0 | 140 [5] | 139 [5] | **0.018** |
| Sodium M1 | 141 [5] | 141 [4] | 0.32 |
| Δ Sodium | 1 [4] | 1 [4] | 0.29 |
| LVEF M0 (%) | 35 [8] | 34 [9] | **<.0001** |
| Age (years) | 64 [17] | 70 [15] | **<.0001** |
| Male | 71 | 64 | **0.014** |
| Caucasian | 91 | 89 | 0.39 |
| Previous hospitalization for HF | 7 | 16 | **<.0001** |
| Reperfusion therapy | 46 | 37 | **0.002** |
| Previous AMI | 26 | 37 | **<.0001** |
| Diabetes | 31 | 39 | **0.005** |
| Prior episodes of HF | 14 | 26 | **<.0001** |
| Hypertension | 61 | 71 | **0.001** |
| **Medications** | | | |
| Eplerenone | 51 | 42 | **0.007** |
| ACEI / ARB | 86 | 89 | 0.17 |
| Beta-blockers | 76 | 70 | **0.017** |
| Loop diuretics | 52 | 79 | **<.0001** |

The events considered between month 1 and month 3 after acute myocardial infarction were cardiovascular death and/or hospitalization for heart failure. Values are expressed as medians [inter-quartile range] or proportions where appropriate.

M0: baseline measurement, M1: measurement at month 1, ΔePVS: plasma volume variation estimated by Strauss formula. See legends of Tables 1 for remaining abbreviations.

* Absolute change between month one and baseline. # Relative change between month one and baseline.

**Table 3: Stepwise logistic regression with ΔePVS**

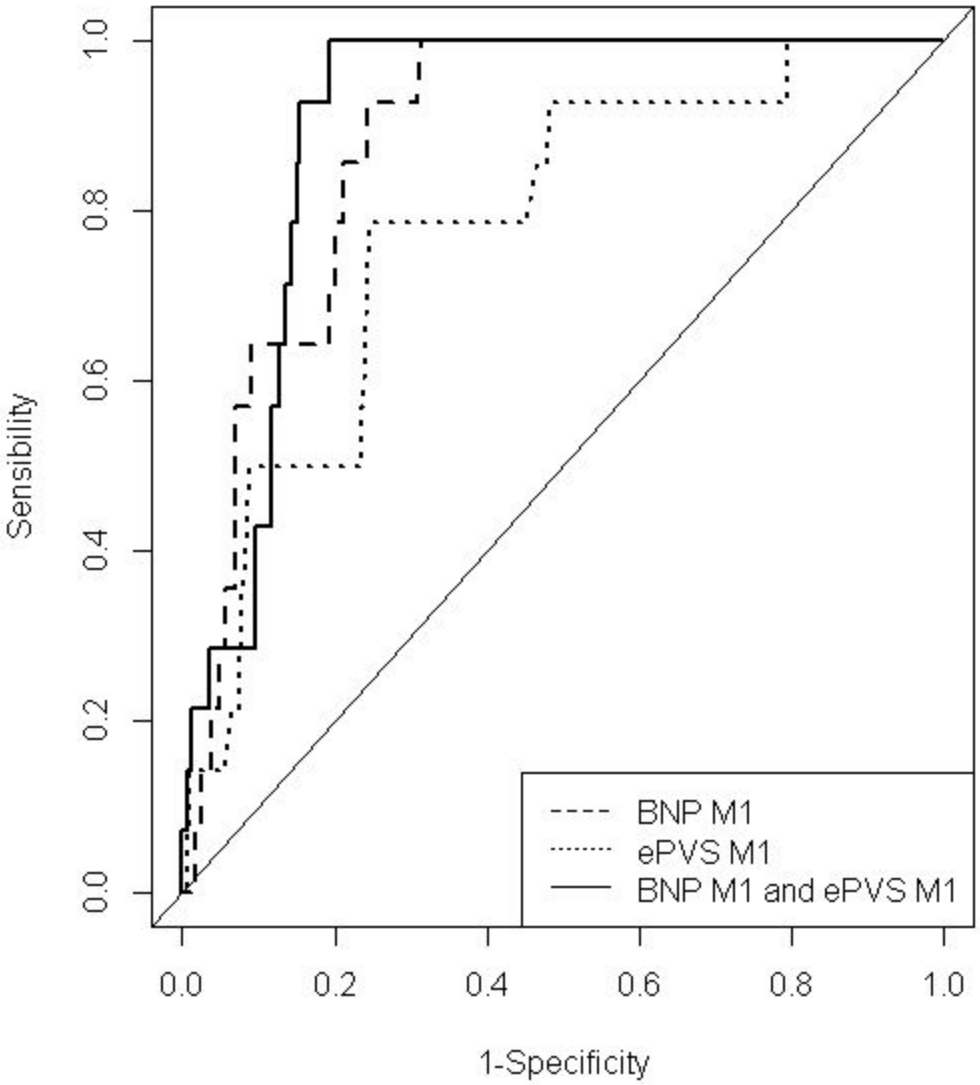
| Variables retained by the model | Coefficient | OR | OR (CI 95 %) | | p |
|---|---|---|---|---|---|
| NYHA M1 ≥ 3 | 1.07 | 2.92 | 2.21 | 3.86 | <0.0001 |
| eGFR M1 | -0.02 | 0.98 | 0.98 | 0.99 | <0.0001 |
| KILLIP M0 ≥ 3 | 0.47 | 1.60 | 1.21 | 2.12 | 0.001 |
| ΔePVS | 0.01 | 1.01 | 1 | 1.02 | 0.004 |
| LVEF M0 | -0.02 | 0.98 | 0.96 | 1 | 0.031 |
| Previous Hospitalization for HF | 0.44 | 1.55 | 1.07 | 2.25 | 0.025 |
| Systolic BP M1 | -0.01 | 0.99 | 0.98 | 1 | 0.005 |
| Hypertension | 0.43 | 1.54 | 1.15 | 2.07 | 0.003 |
| Weight M1 | -0.01 | 0.99 | 0.98 | 1 | 0.043 |

p is a p-value associated to the likelihood ratio test. OR: odds-ratio, CI: confidence interval. See legends of Tables 1 and 2 for abbreviations.

**Table 4: Stepwise logistic regression with ePVS at M1**

| Variables retained | Coefficient | OR | OR (CI 95 %) | | p |
|---|---|---|---|---|---|
| NYHA M1 ≥ 3 | 1 | 2.72 | 2.05 | 3.61 | <0.0001 |
| ePVS M1 | 0.32 | 1.38 | 1.21 | 1.59 | <0.0001 |
| eGFR M1 | -0.01 | 0.99 | 0.98 | 0.99 | 0.0001 |
| KILLIP M0 ≥ 3 | 0.46 | 1.58 | 1.19 | 2.10 | 0.002 |
| LVEF M0 | -0.02 | 0.98 | 0.96 | 1 | 0.030 |
| Previous Hospitalization for HF | 0.43 | 1.53 | 1.06 | 2.22 | 0.030 |
| Hypertension | 0.39 | 1.47 | 1.10 | 1.97 | 0.009 |
| Systolic BP M1 | -0.01 | 0.99 | 0.98 | 1 | 0.008 |

p is a p-value associated to the likelihood ratio test. OR: odds-ratio, CI: confidence interval. See legends of Tables 1 and 2 for abbreviations.


Sensibility
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
BNP M1
ePVS M1
BNP M1 and ePVS M1

**Complete Statistical Analysis section**

All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina) and R software (R Development Core Team, 2005). Continuous variables are described as medians and interquartile range and categorical data as proportions. Chi-square tests or the Fisher exact test were used for categorical variables and nonparametric Kruskal-Wallis tests for continuous variables. Correlations were obtained with Spearman's rho.

**Three formulas of change in plasma volume**

To estimate relative changes in PV between M0 and M1, three different formulas were used. The Strauss formula ( $\Delta$ ePVS) uses changes in hemoglobin and hematocrit concentrations and does not provide an instantaneous measure of PV but its variation between two time points, while the Kaplan and Hakim formulas respectively estimate instantaneous PV taking into account weight and hematocrit concentration at a given time point. The formulas are defined as follows:

(1) $\Delta \text{ePVS} = 100 \times \frac{\text{hemoglobin(M0)}}{\text{hemoglobin(M1)}} \times \frac{1 - \text{hematocrit(M1)}}{1 - \text{hematocrit(M0)}} - 100$ (Strauss formula)

(2) $\text{ePV} = (0.065 \times \text{weight (kg)}) \times (1 - \text{hematocrit})$ (Kaplan formula)

(3) $\text{ePV} = (1 - \text{hematocrit}) \times (a + b \times \text{weight (kg)})$ with a=1530 and b=41 for men, a=864 and b=47.9 for women (Hakim formula)

For the latter two methods, we can then estimate the relative changes in PV as follows

$$\Delta \text{ePV} = \frac{\text{ePV(M1)} - \text{ePV(M0)}}{\text{ePV(M0)}} \times 100$$

**Selection of variables for modeling.**

In order to select the set of predictors for multivariate analysis, an univariate analysis was performed to test the existence of a significant dependence between each of the initial variables and the two-class variable “event / non-event”. A variable was retained if the corresponding p-value was smaller than 0.15. Moreover, any variable highly correlated with another variable and with a less significant p-value was not retained.

Among the three formulas describing changes in PV, only the Strauss formula was retained as potential explanatory variable for entry into the models given that it was highly correlated with the two other formulas (rho=0.82 with Kaplan, rho=0.87 with Hakim) and was the most significant.

The variations in individual hemoglobin and hematocrit values were not retained because of the expected correlations with ΔePVS (rho=-0.97 for hemoglobin variation, rho=-0.94 for hematocrit variation). The same applies for the hemoglobin and hematocrit levels at baseline and M1 which are involved in the calculation of ePVS (at M1, rho=-0.97 with hemoglobin, rho=-0.93 with hematocrit).

With regard to weight variables, weight at M0 was not retained firstly because of its strong correlation with weight at M1 (rho=0.98) and secondly because it was less significant. For the same reasons, eGFR M0 was not retained (rho=0.70), whereas eGFR at M1 was selected.

**Modelisation**

The selected variables were used in two discrimination methods. Since in supervised learning, keeping non discriminant predictors can increase the misclassification error, stepwise logistic regression (which simultaneously performs variable selection and classification) was first

used, after which a stepwise discriminant analysis and a linear discriminant analysis (LDA) were used in order to perform variable selection and classification, respectively.

At the end of the stepwise logistic regression, from which a set of variables is retained, the probability of belonging to the "event" class for each patient can be estimated from the obtained model. If this probability is greater than a given threshold, then the patient is classified into the "event" class.

Sensitivity and specificity were calculated for different values of the threshold and the optimal value minimizing (1-Sensitivity)² + (1-Specificity)² was chosen . The area under the receiver operating characteristic (ROC) curve (AUC) was used as a measure of the quality of the classification.

For the stepwise discriminant analysis, Wilks lambda, which is a class discrimination criterion, was used.

Linear discriminant analysis (LDA), introduced by Fisher, can be presented in a simple geometric framework. Each patient of the sample is represented by a point in a p-dimensional space, the coordinates of which are the values of the p explanatory variables. In the present study, there are two classes of points, namely non-event and event. of which the barycenters $G_0$ and $G_1$ are calculated. For each patient to classify, the values of the explanatory variables are observed and the patient is represented by a point $x$. The distances of this point to the two barycenters, respectively $d_0$ (distance to the "non-event" class) and $d_1$ (distance to the "event" class), are calculated by using the same metric $M=W^{-1}$, the inverse of the within-covariance matrix W of the explanatory variables in the sample of patients. If the difference between these squared distances $d_0^2 - d_1^2$ is greater than an optimal threshold, then this patient is classified into the "event" class. The threshold is determined in the same manner as explained previously.

**Model validation**

Quality checks and stability of classification rules were tested. Sensitivity and specificity were calculated for each method in resubstitution, that is by using the sample of patients from which the classification rule is defined. Given that this particular measure of the quality of a classification rule is generally too optimistic since it is tested on patients who served to build it., a cross-validation was therefore undertaken in order to gain a more accurate measure of quality. In this resampling method, the sample was divided into m classes of patients. One of the m classes being fixed, a classification rule was then established from the other (m-1) classes and applied to the individuals of the fixed class. This is repeated m times by changing at every time the fixed class such that each individual in the sample is classified using a rule to the construction of which the individual did not participate. The sensitivity, specificity and value of criterion are thus calculated which more accurately represent the quality of the rule. A too great difference between these calculated values and those obtained by resubstitution ultimately points to an instability of the model, which in this case is not retained.

**Sensitivity analysis**

Patients in the non-event sample were drawn at random 1000 times, similar to that found in the event sample. By performing stepwise logistic regression on these samples, ePVS M1 was selected 978 times and $\Delta$ ePVS 423 times. Thus it appears that ePVS M1 is a better predictor of early cardiovascular events than $\Delta$ ePVS.

**Supplementary Table 1: Univariate analysis with the three formulas of change in plasma volume**

| Variables | Non-event n=4697 | Event n=260 | p |
|---|---|---|---|
| Δ ePV (Strauss) (%) | -2.3 [19.8] | 0 [20.9] | 0.0009 |
| ePV M0 (Kaplan) (mL) | 2990 [750] | 2938 [777] | 0.2776 |
| ePV M1 (Kaplan) (mL) | 2959 [727] | 2931 [755] | 0.6330 |
| Δ ePV (Kaplan) (%) | -1.7 [9.5] | -1.2 [10.9] | 0.1410 |
| ePV M0 (Hakim) (mL) | 2780 [527] | 2763 [568] | 0.5413 |
| ePV M1 (Hakim) (mL) | 2751 [510] | 2746 [570] | 0.7209 |
| Δ ePV (Hakim) (%) | -1.5 [8.9] | -0.9 [10] | 0.0597 |

The events considered between month 1 and month 3 after acute myocardial infarction were cardiovascular death and/or hospitalization for heart failure. Values are expressed as medians [interquartile range]. p is the p-value associated to the Kruskal-Wallis test.

M0: baseline measurement. M1: measurement at month 1. ePV: estimated plasma volume, Δ ePV: estimated relative change in plasma volume between month one and baseline.

**Supplementary Table 2: Stepwise discriminant analysis and Linear Discriminant Analysis with ΔePVS**

| Variables retained by the model | Coefficient | F (Λ Wilks) | p |
|---|---|---|---|
| NYHA M1 ≥ 3 | 3.4337 | 78.27 | <.0001 |
| eGFR M1 | -0.0331 | 21.20 | <.0001 |
| KILLIP M0 ≥ 3 | 1.2138 | 12.84 | 0.0003 |
| ΔePVS | 0.0243 | 8.82 | 0.0030 |
| LVEF M0 | -0.0495 | 4.73 | 0.0297 |
| Previous Hospitalization for HF | 1.4717 | 8.33 | 0.0039 |
| Hypertension | 0.8356 | 8.69 | 0.0032 |
| Systolic BP M1 | -0.0230 | 10.40 | 0.0013 |
| Weight M1 | -0.0195 | 4.75 | 0.0294 |

p is the p-value associated to the Wilks lambda test. "Coefficient" stands for "Coefficient of the variable in the difference $d_0^2 - d_1^2$ "

BP: blood pressure, HF: heart failure, eGFR: estimated glomerular filtration rate, ΔePVS: plasma volume variation estimated by the Strauss formula, LVEF: left ventricular ejection fraction, M0: baseline measurement, M1: measurement at month 1, NYHA: New York Heart Association functional class.

**Supplementary Table 3: Measure of the quality and stability of the models by resubstitution and cross-validation.**

| | | Selection with ΔePVS | | Selection with ΔePVS removed | |
|---|---|---|---|---|---|
| | | LR | LDA | LR | LDA |
| Res | AUC | 0.7474 | 0.749 | 0.7462 | 0.7463 |
| | Th* | 0.0481 | -0.5529 | 0.0442 | -0.4761 |
| | Sp | 0.6904 | 0.6909 | 0.6449 | 0.7090 |
| | Se | 0.7346 | 0.7385 | 0.7654 | 0.7000 |
| | Cr | 0.1663 | 0.164 | 0.1812 | 0.1747 |
| VC4 | Sp | 0.693 | 0.6887 | 0.6715 | 0.6977 |
| | Se | 0.7038 | 0.7038 | 0.7038 | 0.6808 |
| | Cr | 0.182 | 0.1846 | 0.1956 | 0.1933 |
| VC10 | Sp | 0.6947 | 0.6907 | 0.6921 | 0.7079 |
| | Se | 0.7038 | 0.7115 | 0.6615 | 0.6846 |
| | Cr | 0.1809 | 0.1789 | 0.2093 | 0.1848 |

ΔePVS: plasma volume variation estimated by the Strauss formula, LR: logistic regression, LDA: linear discriminant analysis, AUC: area under ROC curve, Cr: criterion $(1\text{-Se})^2 + (1\text{-Sp})^2$, Res: Resubstitution, Se: sensitivity, Sp: specificity, Th*: optimal threshold, VC4: 4 fold cross-validation, VC10: 10 fold cross-validation.

**Supplementary Table 4: Subgroup analyses: stepwise logistic regression including ΔePVS or ePVS M1.**

| Subgroups | | LR with ΔePVS | | LR with ePVS M1 | |
|---|---|---|---|---|---|
| | | OR (CI 95 %) | p | OR (CI 95 %) | p |
| Anemia | With (n=1544, 105 events) | 1.0198 (1.0065 - 1.0333) | 0.0043 | 1.5872 (1.2932 – 1.9481) | <.0001 |
| | Without (n=3413, 155 events) | 1.0145 (1.0046 - 1.0246) | 0.0051 | 1.4751 (1.1784 – 1.8465) | 0.0009 |
| Anticoagulants | With (n=743, 49 events) | 1.0235 (1.0069 – 1.0404) | 0.0062 | 1.6249 (1.1968 – 2.2061) | 0.0024 |
| | Without (n=4174, 211 events) | not selected | 0.0599 | 1.3521 (1.1603 – 1.5757) | 0.0002 |
| Antithrombotics | With (n=2013, 93 events) | 1.0156 (1.0038 – 1.0275) | 0.0112 | 1.4050 (1.1174 – 1.7667) | 0.0045 |
| | Without (n=2944, 167 events) | not selected | 0.0773 | 1.4007 (1.1808 – 1.6615) | 0.0001 |
| Reperfusion therapy | With (n=2270, 95 events) | 1.0134 (1.0016 – 1.0253) | 0.0295 | 1.4208 (1.1386 – 1.7730) | 0.0027 |
| | Without (n=2687, 165 events) | 1.0106 (1.0009 – 1.0204) | 0.0339 | 1.4302 (1.1935 – 1.7140) | 0.0001 |

p is the p-value associated to the likelihood ratio test. When the variable was not retained in the final model (-), p corresponds to the last p-to-enter value. ΔePVS: plasma volume variation estimated by the Strauss formula, ePVS: plasma volume estimated by the Strauss formula-derived formula, M1: measurement at month 1, OR: odds-ratio. CI: confidence interval.